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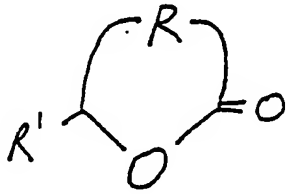
(54) Title: POTASSIUM CHANNEL ACTIVATING COMPOUNDS AND METHODS OF USE THEREOF



(I)

(57) Abstract

A method for activating potassium channels and for treating hypertension, addiction, asthma, incontinence, and other conditions treatable by potassium channel activators, comprising administering a compound having formula (I), wherein R is a saturated or unsaturated group having from 1 to 4 carbon atoms which is optionally substituted by lower alkyl, lower alkenyl or lower alkoxy groups; and wherein R' is hydrogen, lower alkyl, lower alkenyl, or aralkyl.

POTASSIUM CHANNEL ACTIVATING COMPOUNDS AND METHODS OF USE THEREOF

Field of the Invention

The present invention relates to compounds and compositions which have been found useful in potassium channel activation, treatment of hypertension, alleviation of the symptoms of addition withdrawal, and all other conditions treatable by a potassium channel opener, and to methods of use of these compounds.

Background of the Invention

Avena sativa, or common oats, is an annual grain which is widely cultivated for its edible grain, sometimes called groats. Beneficial properties have long been attributed to oats, as evidenced by such common expressions as "feeling your oats." Persons who ascribe to "natural medicine" or "herbal science" have included oats in their armamatum of purportedly therapeutic preparations. Indeed, over the years scattered reports of pharmacological activity attributable to some component in oats have appeared in the traditional scientific literature, most recently with respect to the cholesterol-lowering properties of oat bran.

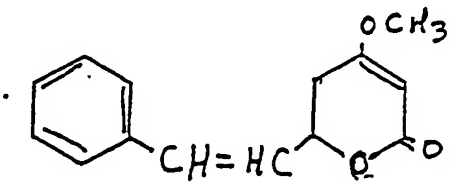
There have been reports in the popular literature of the use of alcoholic extracts of *Avena sativa* as treatments for both opiate addiction and cigarette smoking. However, the scientific literature has not documented any anti-addictive activity of any of the chemically defined compounds in *Avena sativa*.

Handler, in The Doctors' Vitamin and Mineral Encyclopedia, Simon and Schuster, New York, 1990, 318-319, notes that there have been claims that oats have anti-depressant and aphrodisiac properties, and there is some evidence that oats can aid people in overcoming drug habits. A decoction of common oats has been successfully used in Ayurvedic medicine to treat opium addiction. It

methyl group for the hydroxymethyl group of the aglycone A.

Erickson, in Photochem. Photobiol. 49(4): 479-483, 1989, disclose the visualization of a highly purified photochrome from *Avena sativa* by electron microscopy after negative staining with uranyl acetate and after rotary shadowing with platinum. The particle shape was variable in both types of specimens, but tripartite structures resembling a "Y" were consistently observed. The tripartite substructure is composed of three globular domains, each having a diameter of 7 to 8 nm and equally spaced in an equilateral triangle. The dimensions of the tripartite particle measured 15 nm between the centers of any two of the three particles. When the phytochrome was digested with trpysin to release the amino-terminal globular domain from the polypeptide, the tripartite structure was lost. It was proposed that the outer particles of the tripartite structure are the amino-terminal domains of the phytochrome dimer, and the central particle comprises the carboxyl domains of the two subunits.

The tetrahydropyranone structure is a major feature of a series of aromatic compounds obtained from *piper methysticin Forst*, the Polynesian kava-kava plant, also known as intoxicating pepper. A number of aromatic pyrones have been identified in kava-kava extracts; all of these compounds are unsaturated across the 3,4-positions and contain a methoxy group in the 4-position:



dosage. The effective dose was between 5 and 10 mg/kg. The lethal dose was between four and ten times higher for i.v. administration, and about 1 gram/kg for oral administration. These results suggest a neurotransmitter mediated mechanism due to the antagonism by reserpine, and possibly an effect on membrane channels to account for the procaine-like effects.

In Arch. Int. Pharmacodym 180: 475-491, 1969, Kretzschmar et al. report studies of the spasmolytic activities of the kava-pyrones using the guinea pig isolated ileum preparation. All six of the kava compounds were found to have spasmolytic activity. Histamine, 5-HT, acetylcholine and nicotine were used to induce muscle contractions, and the ability of the kava pyrones to antagonize this activity was tested. The kava-pyrones were found to antagonize the effects of all of the stimulants. Thus, the mechanism of the kava-pyrones was not due to a specific receptor-mediated mechanism at the transmitter level but were considered to be direct musculotropic actions similar to that of papaverine. The kava-pyrones were most potent against contractions due to nicotine and 5-HT, and less active against acetylcholine and histamine. The authors again attempted to compare the results with those obtained by local anesthetics, and found the highest correlation with benzocain and cocaine and less correlation with procaine. There was a clear relationship between structure and activity for the kava pyrones: compounds which are completely saturated in the pyrone ring, i.e., the tetrahydropyrones, were more effective than compounds that were saturated in the 5,6-position, the dihydropyrones. Substitution on the benzene ring of these compounds was found to alter their activity. No compounds lacking the 4-methoxy group on the pyrone ring were tested.

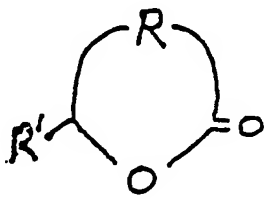
Gamma and delta lactones are known to be flavor and fragrance compounds. Methods of producing such lactones are disclosed, for example, in Page et al., PCT

It is still another object of the present invention to provide methods for alleviating the symptoms of withdrawal from an addictive substance.

It is yet another object of the present invention to provide a method for treating any condition which may be alleviated by potassium channel activation.

It is yet a further object of the present invention to provide a method for activating potassium channels in vivo.

It has been discovered that compounds of the following formula have the property of potassium channel activation:



wherein R is a saturated or unsaturated moiety of one to four carbon atoms, so as to create a four- to seven-membered ring structure, which ring structure may be saturated or unsaturated, and the carbon atoms of which may be substituted by lower alkyl,lower alkenyl groups or lower alkoxy groups, and R' may be hydrogen, lower (e.g., C_1-C_8) alkyl, lower alkenyl or aralkyl in which the alkyl portion is preferably lower alkyl.

The compounds of the present invention may be used to treat withdrawal symptoms from any addictive substance, such as cigarettes, alcohol or narcotic drugs. As this utility has been discovered to be an effect of the potassium channel activation properties of these compounds, any compounds known to be a potassium channel activator can be used for the treatment of withdrawal symptoms from addictive substances. Non-limiting examplesunds having the property of potassium channel activation are RP 52891, cromakalim, lemakalim, celikalim, RO-316930, 507-PC0-400, HOE-234, minoxidil, diazoxide, pinacidil, and nicorandil.

This activity has never been reported for *Avena sativa*, perhaps because of the pronounced stimulant activity of previously used extracts, which might have masked the hypotensive activity.

The hypotensive agent may be further purified from the extract using organic extraction techniques. Initially, the distillate is made basic using 5% sodium carbonate and extracted with ethyl acetate. The active compound is found to reside in the mother liquor, and need not be extracted. The water phase is then acidified using concentrated hydrochloric acid and again extracted with ethyl acetate. Again, the active compound need not be extracted.

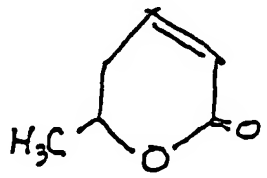
After HPLC, the mother liquor is sufficiently pure to perform structural studies. The water phase is dried by lyophilization and subjected to NMR and mass spectral analysis. The active compound proves to be a substituted tetrahydropyran, 6-methyl-tetrahydropyran-2-one.

Isolated avena pyrone was studied for its action against ionic channels in cell membranes using the lipid bilayer technique. Membranes from rat brain were fused with a lipid bilayer formed across the opening of a patch-clamp pipette. Electrical activity was monitored using an Axon Instruments Axopatch amplifier using 100 mM symmetrical KCl solutions. In the presence of elevated levels of calcium, at least three types of potassium channel can be determined: a small 25-50 pS channel, a 90-120 pS channel, and a large 200-220 pS channel. In the absence of calcium in the bathing solutions, openings of the large 200 pS channel are rarely seen. When avena pyrone is added to the bathing solution, an activation of the large K^+ channel is seen, evidenced by an increased open probability and very long open times.

Figures 1 and 2 show the exposure of the channels to potassium in the presence of avena pyrone. In the two tracings in Figure 1, the membrane potential was

one experiences upon withdrawal from an addictive substance.

Besides the avena pyrone, another known natural compound having the structure of the present invention is parasorbic acid (or parasorbinic acid), which is the dihydro analog of avena pyrone and has the following structure:



Parasorbic acid is a natural product which has been isolated from the berries of mountain ash (Rowan), or *Sorbus aucuparia L.*, Rosaceae. The juice of the berries has been used as an astringent and as a mouthwash. The berries contain a high concentration of vitamin C and are also considered to to be anti-scorbutic as well as a mild diuretic. In northern Europe, a strong spirit is made from Rowan berries. Parasorbic acid is the major, if not exclusive, product obtained by steam distillation of acidified berries.

The antispasmodic effect of aryl-substituted α-pyrones from the kava-root have previously been reported, although it was not known that these effects were due to the property of potassium channel activation. It has now been confirmed that kawain is indeed a potassium channel activating substance. All of the kava pyrones have a bulky aromatic group. It has unexpectedly been found that the substitution of a lower alkyl group for the more bulky aromatic group enhances the potassium channel activation effects of the compounds.

While the kava pyrones were known to have anti-convulsant and anti-spasmodic properties, it was not known that they had potassium channel activation effects, and therefore it would not have been obvious from their known anti-convulsive and anti-spasmodic effect that they could also be used for the treatment of hypertension or the treatment of addiction withdrawal symptoms, or any of the

granulating, dragee-making, dissolving, or lyophilizing processes. Thus, pharmaceutical preparations for oral use can be obtained by combining the active compounds with solid excipients, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired or necessary, to obtain tablets of dragee cores.

Examples of suitable excipients include lactose, sucrose, mannitol, sorbitol, cellulose preparations, calcium phosphates, binders such as starch paste from maize starch, wheat starch, rice starch, potato starch, gelatin, tragacanth, methyl cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose and/or polyvinylpyrrolidone. If desired, disintegrating agents may be added, such as the above-mentioned starches as well as carboxymethyl starch, crosslinked polyvinyl pyrrolidone, agar, alginic acid, sodium alginate, and the like.

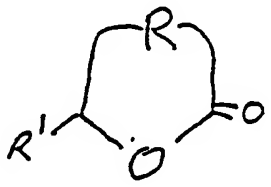
Auxiliaries include flow-regulating agents and lubricants such as silica, talc, stearic acid or salts thereof and/or polyethylene glycol. Dragee cores are provided with suitable coatings which, if desired, are resistant to gastric juices. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions and suitable organic solvents or solvent mixtures.

In order to produce coatings resistant to gastric juices, solutions of suitable cellulose preparations such as acetyl cellulose phthalate of hydroxypropylmethylcellulose phthalate are used. Dyestuffs or pigments may be added to the tablets or dragee coatings, for example, for identification or in order to characterize different combinations of active compound doses.

can range from several days to treat addiction to administration periodically, e.g., weekly, to treat hypertension. The dosage required for each patient may vary widely, depending upon the degree of hypertension or addiction treated and the individual patient response. However, in general, a dosage of from about 0.1 to about 10 mg/kg body weight is appropriate for most patients.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and therefore such adaptations and modifications are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology herein is for the purpose of description and not of limitation.

5. A method for treating a condition treatable by means of a potassium channel activator, comprising administering to a patient in need of a potassium channel activator an effective amount of compound having the formula:



wherein R is a saturated or unsaturated group having from 1 to 4 carbon atoms which is optionally substituted by lower alkyl, lower alkenyl or lower alkoxy groups, and

wherein R' is selected from the group consisting of hydrogen, lower alkyl, lower alkenyl, and aralkyl.

6. A method in accordance with claim 5 wherein R' is hydrogen, lower alkyl or lower alkenyl.

7. A method for alleviating the symptoms of addiction withdrawal, comprising administering to a patient in need thereof an effective amount of a compound having the properties of potassium channel activation.

INTERNATIONAL SEARCH REPORT

PCT/US92/09194

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/335, 31/35, 31/34

US CL :514/449, 450, 460, 473, 474

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/449, 450, 460, 473, 474; 514/812, 813

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Nature vol. 233, October 15, 1971, Cl. L. Anand, "Effect of Avena Sativa on Cigarette Smoking", p. 496.	3-7
A	J. Pharm Pharmac. (27), 1975, M. Grieve, "The Medicinal, Culinary, Cosmetic, and Economic Properties, Cultivation and Folk-Lore of Herbs, Grassess, Fungi, Shrubs, and Trees, with all their Modern Scientific Uses", p. 92-98.	1-7
A	The Doctor's Vitamin and Mineral Encyclopedia, Sheldon Saul Hendler, pp. 318-319 and 597-598.	1-7

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 01 DECEMBER 1992	Date of mailing of the international search report 15 JAN 1993
Name and mailing address of the ISA/ US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. NOT APPLICABLE	Authorized officer for WILLIAM JARVIS Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

Int...ational application No.
PCT/US92/09194

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

STN: Registry (structure). Chem-Abstract, Biosis; Dialog; APS. Search terms: Structure of claim 1 and parasorbic acid and 2H-6-methyltetrahydropyran -2- one as/for: (1) potassium channel activator, (2) treatment of hypertension, (3) treatment of withdrawal, craving addiction.